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# Cerebral Venous Sinus Thrombosis - Diagnostic Strategies and Prognostic Models: A Review

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## 1. Introduction

In 1825, Ribes described a case of a 45-year old man who died after a 6-month history of epilepsy, seizures and delirium. The autopsy examination revealed thrombosis of the superior sagittal sinus, the left lateral sinus and a cortical vein in the parietal region. This was probably the first detailed description of extensive cerebral venous sinus thrombosis (CVST). Since then, the literature describing this disease has comprised of case reports, series and some newer prospective studies, including recent reviews and guidelines (statement) on the diagnosis and management of CVST (Siddiqui & Kamal, 2006; Stam, 2005; Saposnik et al, 2011; Brown & Thore, 2011).

The cerebral venous sinus thrombosis is a challenging condition and it is most common than previously thought. CVST accounts for 0.5% to 1.0% of all strokes and usually affects young individuals. Important advances have been made in the understanding of the pathophysiology of this vascular disorder. The diagnosis of CVST is still frequently overlooked or delayed as a result of the wide spectrum of clinical symptoms and the often sub-acute or lingering onset. Patients with CVST commonly present with headache, although some develop a focal neurological deficit, decreased level of consciousness, seizures, or intracranial hypertension without focal neurological signs. Uncommonly, an insidious onset may create a diagnostic challenge. The main problem of this disorder is that it is very often unrecognised at initial presentation. In particular, a prothrombotic factor or a direct cause is identified in approximately 66% of the CVST patients (a list of most important causal and risk factors are listed in **Table 1**).

Cerebral venous thrombosis is more common in women than men, with a female to male ratio of 3:1 (cited in Ferro & Canhao, 2011). The imbalance may be due to the increased risk of CVST associated with pregnancy and puerperium and with oral contraceptives. The female predominance in CVST is found in young adults, but not in children or older adults.

Genetic prothrombotic conditions
Antithrombin deficiency <sup>5</sup>
Protein C and protein S deficiency <sup>6-8</sup>
Factor V Leiden mutation <sup>9-11</sup>
Prothrombin mutation (the substitution of A for G at position 20210) <sup>9,11,12</sup>
Homocysteinemia caused by gene mutations in methylenetetrahydrofolate reductase <sup>13,14</sup>
Acquired prothrombotic states
Nephrotic syndrome
Antiphospholipid antibodies <sup>7,15</sup>
Homocysteinemia <sup>14</sup>
Pregnancy <sup>16,17</sup>
Puerperium <sup>17</sup>
Infections
Otitis, mastoiditis, sinusitis <sup>6</sup>
Meningitis
Systemic infectious disease <sup>6</sup>
Inflammatory disease
Systemic lupus erythematosus <sup>18</sup>
Wegener's granulomatosis <sup>8</sup>
Sarcoidosis
Inflammatory bowel disease
Behçet's syndrome <sup>19,20</sup>
Hematologic conditions
Polycythemia, primary and secondary
Thrombocythemia
Leukemia <sup>21</sup>
Anemia, including paroxysmal nocturnal hemoglobinuria <sup>22</sup>
Drugs
Oral contraceptives <sup>9,23</sup>
Asparaginase <sup>6,21</sup>
Mechanical causes, trauma

Table 1. Most important causes of and risk factors associated with cerebral venous sinus thrombosis. *Reproduced with the written permission from the paper by Stam (2005).*

In the prospective International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVST) cohort of 624 adults with CVST, women comprised 465 (75%) of the patients. Compared with men, women had significantly lower mean age (42 vs 34 years). Furthermore, a gender specific risk factor — oral contraceptives, pregnancy, puerperium, and hormone replacement therapy — was identified in 65% of the women. CVST is more common in neonates than it is in infants, children or adults. In adults, CVST affects patients who are younger on average than those with arterial types of stroke. In the ISCVST, the mean age of patients with CVST was 39 years, and only 8% of them were older than 65 years (Ferro & Canhao, 2011). Topographically, the most frequent occurrence of CVST has been observed in the superior sagittal sinus (62%) followed by the transverse (lateral) sinus (41-45%) (**Figure 1**).

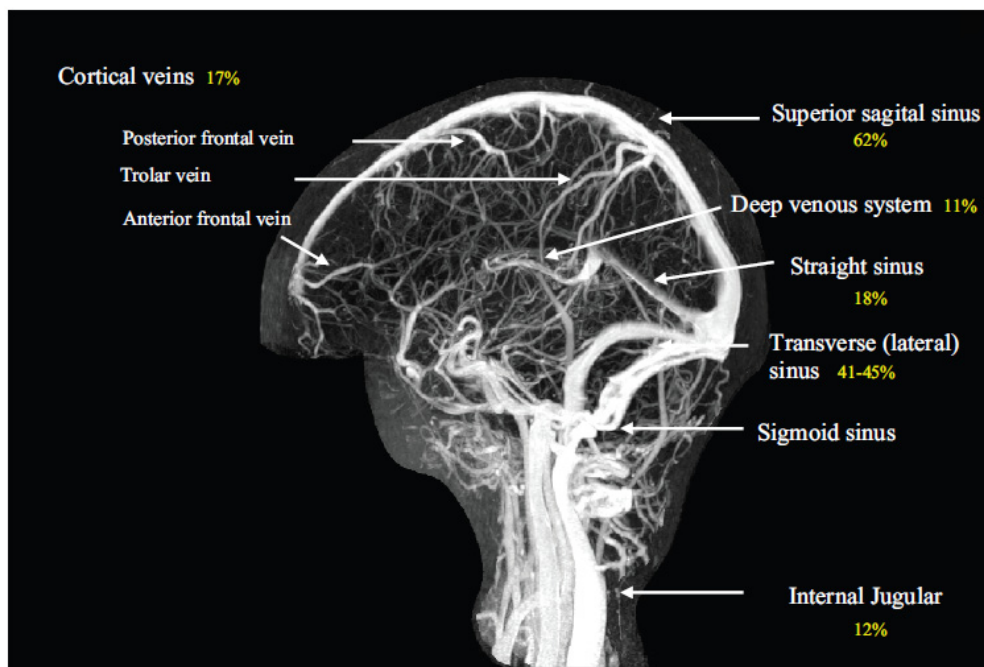


Fig. 1. MRI venogram of the cerebral venous system and most frequent location of CVST. Reproduced with the written permission from the paper by Saposnik *et al.* (2011) as derived from data on 624 patients in the International Study on Cerebral Venous and Dural Sinuses Thrombosis as reported by Manolidis & Kutz (2005).

The pathogenesis of CVST remains incompletely understood because of the high variability in the anatomy of the venous system, and the paucity of experiments in animal models of CVST. However, there are at least two different mechanisms that may contribute to the clinical features of CVST: a) *thrombosis of cerebral veins or dural sinus leading to cerebral parenchymal lesions or dysfunction*; and b) *occlusion of dural sinus resulting in decreased cerebrospinal fluid (CSF) absorption and elevated intracranial pressure*. (**Figure 2**). Obstruction of the venous structures may result in increased venous pressure, decreased capillary perfusion pressure, and increased cerebral blood volume. Dilatation of cerebral veins and recruitment of collateral pathways play an important role in the early phases of CVST and may initially compensate for changes in pressure. The increase in venous and capillary pressure leads to blood-brain barrier disruption, causing vasogenic edema, with leakage of blood plasma into the interstitial space. As intravenous pressure continues to increase, mild parenchymal changes, severe cerebral edema, and venous hemorrhage may occur due to venous or capillary rupture. The increased intravenous pressure may lead to an increase in intravascular pressure and a lowering of cerebral perfusion pressure, resulting in decreased cerebral blood flow (CBF) and failure of energy metabolism. In turn, this allows intracellular entry of water from failure of the  $\text{Na}^+/\text{K}^+$  ATPase pump, and consequent cytotoxic edema (Ferro & Canhao, 2011).

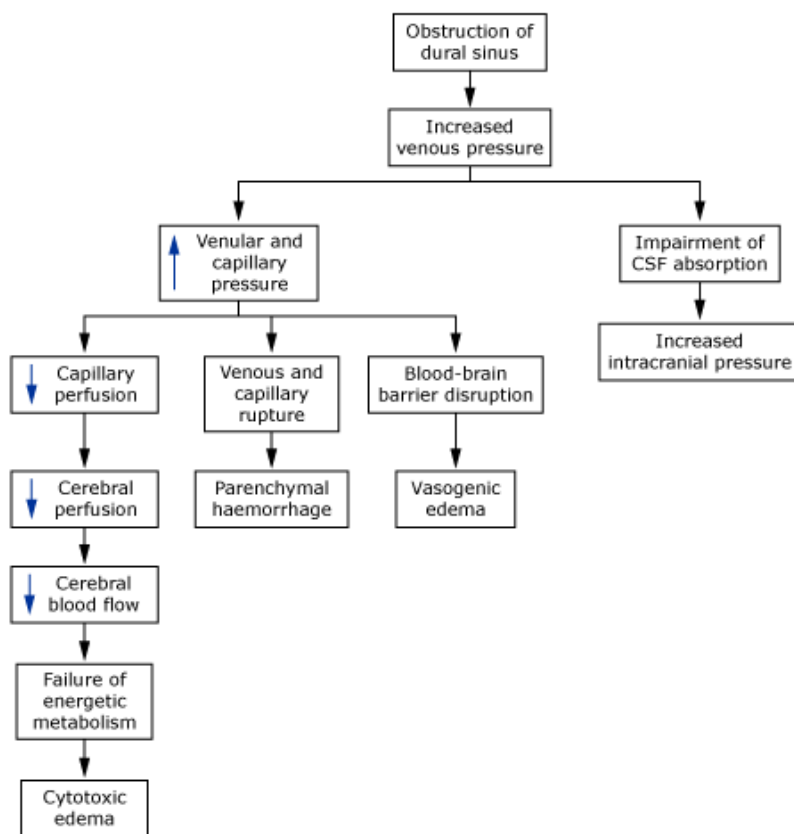


Fig. 2. Possible mechanisms of the development of CVST. *Reproduced with the written permission from the paper by Ferro & Canhao (2011).*

Advances in our understanding of the venous occlusion pathophysiology have been achieved by the use of newer magnetic resonance imaging (MRI) methods, mainly diffusion-weighted MRI (DWI) and perfusion-weighted MRI (PWI). These techniques have demonstrated the coexistence of both cytotoxic and vasogenic edema in patients with CVST. The other effect of venous thrombosis is impairment of CSF absorption. Normally, CSF absorption occurs in the arachnoid granulations (Leach et al, 2008), which drain CSF into the superior sagittal sinus. Thrombosis of the dural sinuses leads to increased venous pressure, impaired CSF absorption, and consequently elevated intracranial pressure. Elevated intracranial pressure is more frequent if superior sagittal sinus thrombosis is present, but it may also occur with thrombosis of the jugular or lateral sinus, producing a rise of pressure in the superior sagittal sinus.

As shown in Table 1, many causes or predisposing conditions are associated with CVST. The major risk factors for CVST in adults can be grouped in two classes: *transient* or *permanent* (Table 2). In more than 85% of the adult patients, at least one risk factor for CVST can be identified, most often a prothrombotic condition as mentioned above. In the ISCVST cohort, a prothrombotic condition was found in 34%, and a genetic prothrombotic condition

was found in 22% of all patients. Although infectious causes of CVST were frequently reported in the past, they are responsible for only 6 to 12 percent of cases in modern-era studies of adults with CVST. As with venous thrombosis in other parts of the body, multiple risk factors may be found in about half of adult patients with CVST. No underlying etiology or risk factor for CVST is found in approximately 13% of adult patients. However, it is important to continue searching for a cause even after the acute phase of CVST, as some patients may have a condition such as the antiphospholipid syndrome (APS), polycythemia, thrombocythemia, or malignancy that is discovered weeks or months after the acute phase. It should be noted that the risk for CVST is influenced by the individual's genetic background. In the presence of some prothrombotic conditions, patients are at an increased risk of developing CVST when exposed to a precipitant such a head trauma, lumbar puncture, jugular catheter placement, pregnancy, surgery, infection, and drugs. These prothrombotic conditions include the following: antithrombin deficiency, protein C deficiency or protein S deficiency, Factor V Leiden mutation or G20210 A prothrombin gene mutation.

Transient risk factors	Permanent risk factors
<b>Infection</b> Central nervous system Ear, sinus, mouth, face, and neck Systemic infectious disease  <b>Pregnancy and puerperium</b>  <b>Other disorders</b> Dehydration  <b>Mechanical precipitants</b> Head injury Lumbar puncture Neurosurgical procedures Jugular catheter occlusion  <b>Drugs</b> Oral contraceptives Hormone replacement therapy Androgens Asparaginase Tamoxifen Glucocorticoids	<b>Inflammatory diseases</b> Systemic lupus erythematosus Behçet disease Granulomatosis with polyangiitis (Wegener's) Tromboangiitis obliterans Inflammatory bowel disease Sarcoidosis  <b>Malignancy</b> Central nervous system Solid tumour outside central nervous system Hematologic  <b>Hematologic condition</b> Polycythemia, thrombocythemia Anemia, including paroxysmal nocturnal hemoglobinuria  <b>Central nervous system disorders</b> Dural fistulae  <b>Other disorders</b> Congenital heart disease Thyroid disease

Table 2. Classification of systemic and local conditions increasing the risk of cerebral venous thrombosis. *Reproduced with the written permission from the paper by Ferro & Canhao (2011).*

In particular, the most frequent risk factor in young women is the use of oral contraceptives. Two case-control studies have shown an increased risk of sinus thrombosis in women who use oral contraceptives. Furthermore, the risk for CVST in women using oral contraceptives is increased if they have a prothrombotic defect. In elderly CVST patients, the proportion of cases without identified risk factors is higher (37%) than it is in adults <65 years of age. The most common risk factors in those  $\geq 65$  years old are genetic or acquired thrombophilia, malignancy, and hematologic disorders such as polycythemia (Ferro & Canhao, 2011; Plata et al, 2002).

## 2. Methods

*Search strategy.* For the purpose of this review, a systematic search of the literature databases (e.g., PubMed) by the EndNote software as well as other reference and electronic databases (e.g., Cochrane Library) have been searched by specifically chosen MESH terms, back to 1960. In total, while using the main four single terms (“cerebral”, “sinus”, “venous”, “thrombosis”) and combinations thereof, 4049 peer-reviewed titles have been initially found which have been later reduced down to 43 titles, among which 25 review papers have been also identified. Many references for this review came from the authors’ own archives. Two of us (PAA, BDD) independently reviewed all 43 titles for inclusion as retrieved as above and 35 of them were decided to be included. Additionally, through hand-searching the references of the selected articles and other relevant electronic sources (e.g., Google Scholar), several additional relevant titles were also reviewed for inclusion. Finally, out of the initially 4049 identified titles and all other relevant titles, 39 articles were studied and included in this review. Any disagreements between the original reviewers have been resolved by a third, blinded reviewer (NTC); any further discrepancies have been solved by an open consensus among all of the reviewers.

## 3. Results

Most of the articles that were identified were case reports or limited case series. Others were original articles and reviews or overviews. We were able to initially identify 4049 peer-reviewed titles in PubMed, including 25 review papers. To note, we were able to identify separately only 3 systematic reviews in the Cochrane Library (Ciccone et al, 2004; Kwan & Gunther, 2006; Stam et al, 2002 as cited in Stam, 2005). Finally, 39 articles were included for the purposes of this review.

### 3.1 Early clinical detection and diagnostic strategies with imaging in CVST

**Clinical signs and symptoms and laboratory tests.** The diagnosis of CVST is typically based on a clinical suspicion and imaging confirmation. Clinical findings in CVST usually fall into 2 major categories: a) *focal brain injury from venous ischemia/infarction or hemorrhage* and b) *increased intracranial pressure attributable to impaired venous drainage*. Headache, generally indicative of an increase in intracranial pressure, is the most common symptom in CVST (in 90% of the patients in the ISCVST). The headache of CVST is typically described as diffuse and often progresses in severity over days to weeks. A minority of patients may present with thunderclap headache (Saposnik et al, 2011), suggestive of subarachnoid hemorrhage (SAH) (Atanassova et al, 2006), and a migrainous type of headache has been described. Isolated headache without focal neurological findings or papilledema occurs in up to 25% of the patients with CVST and presents a significant diagnostic challenge. CVST is an



important diagnostic consideration in patients with headache and papilledema or diplopia (caused by sixth nerve palsy) even without other neurological focal signs. When a focal brain injury occurs, most common are hemiparesis and aphasia, but other cortical signs and sensory symptoms may be also observed, together with psychosis in such cases. The clinical manifestations of CVST may also depend on the location of the thrombosis as mentioned above (Figure 1). The superior sagittal sinus is most commonly involved. For the lateral sinus thromboses, as a second prevalent location, the symptoms related to an underlying condition (middle ear infection) may be noted, including constitutional symptoms, fever, and ear discharge. Pain in the ear or mastoid region and headache are typical. On examination, an increased intracranial pressure and distention of the scalp veins may be noted (hemianopia, contralateral weakness, and aphasia may sometimes be seen owing to cortical involvement). Approximately 16% of the patients with CVST have thrombosis of the deep cerebral venous system (internal cerebral vein, vein of Galen, and straight sinus), which can lead to thalamic or basal ganglial infarction (van der Bergh et al, 2005). Most patients present with rapid neurological deterioration (Saposnik et al, 2011). Importantly, several principal clinical features distinguish CVST from other cerebrovascular diseases (CVD). Notably, the focal or generalized seizures are frequent, occurring in about 40% of patients; and, secondly, as a clinical correlate to the anatomy of cerebral venous drainage, the bilateral brain involvement is not infrequent. The latter is particularly notable in cases that involve the deep venous drainage system, when bilateral thalamic involvement may occur, causing alterations in level of consciousness without focal neurological findings. Bilateral motor signs, including paraparesis, may also be present due to sagittal sinus thrombosis and bihemispheric injury. Finally, patients with CVST often present with slowly progressive symptoms. It has to be underlined that very frequently the delays in diagnosis of CVST are common and significant. In the ISCVST, symptom onset was acute (<48 hours) in 37% of patients, subacute (>48 hours to 30 days) in 56% of patients, and chronic (>30 days) in 7% of the patients. The median delay from the onset of symptoms to the hospital admission was 4 days, and from symptom onset to the diagnosis - 7 days.

**Specific diagnostic cues.** About 40% of the patients with CVST present with *intracranial hemorrhage* (ICH). The features suggestive of CVST as a cause of ICH include prodromal headache (which is highly unusual with other causes of ICH), bilateral parenchymal abnormalities, and clinical evidence of a hypercoagulable state. These features may not be present, however, and a high index of clinical suspicion is necessary. An isolated subarachnoid hemorrhage may also occur due to CVST, although this is rare (0.8% of patients in ISCVST). A second specific occurrence is *isolated headache/idiopathic intracranial hypertension* - for example, 25% of the CVST patients may present with isolated headache, and another 25% - with headache in conjunction with papilledema or sixth nerve palsies suggestive of idiopathic intracranial hypertension. In a series of 131 patients who presented with papilledema and clinically suspected idiopathic intracranial hypertension, 10% had CVST at MRI/magnetic resonance venography (MRV). Imaging of the cerebral venous system has been recommended for all patients with the clinical picture of idiopathic intracranial hypertension. Regarding headache - it is an extremely common symptom, and most patients with isolated headache will not have CVST. The cost-effectiveness and yield of routine imaging are highly uncertain. Factors that may suggest the diagnosis, and thus prompt imaging evaluation, include a new, atypical headache; headache that progresses steadily over days to weeks despite conservative treatment; and thunderclap headache, especially if a hypercoagulable state is also present. A third difficult occurrence in CVST is when the patients present with *somnolence or a confusional*

*state in the absence of obvious focal neurological abnormalities* (more common in the elderly and with thrombosis of the deep venous system). Although a number of mechanisms may underlie this clinical presentation, an important cause is bilateral thalamic lesions due to involvement of the deep venous system. Early CT scanning may not be useful; MRI will usually demonstrate abnormalities in such cases (Saposnik et al, 2011).

**Laboratory and other biochemical tests.** A complete blood count, chemistry panel, sedimentation rate, and measures of the prothrombin time and activated partial thromboplastin time are indicated for suspected CVST. These may be indicative of hidden hypercoagulable state, infectious process or inflammatory state as contributing factors to the CVST development. Further, the examination of the cerebrospinal fluid (CSF) is typically not helpful in cases with focal neurological abnormalities and radiographic confirmation of the diagnosis of CVST unless there might be a suspicion of meningitis. An elevated opening pressure may be a clue for diagnosing CVST in patients who present with headaches (i.e., such pressure may be present in >80% of the patients). Elevated cell counts may be present in about 50% of the patients and the increased protein levels - in about 35%, however, their absence should not exclude a consideration of CVST. Usually, there are no specific CSF abnormalities in CVST. Additionally to the above routine tests, the D-dimer, a product of fibrin degradation, has a diagnostic role in exclusion of DVT or pulmonary embolus when used with pre-test probability assessment. In a well-designed prospective, multicenter study of 343 patients presenting to the emergency department with symptoms that suggested CVST, a positive D-dimer level (defined as a level >500µg/l) was found in 34 of 35 patients with confirmed CVST and 27 of 308 patients without CVST (sensitivity >97% and specificity >90%). Having a negative predictive value of 99.6% a normal D-dimer level test may easily help identify patients with a low probability of CVST. Several factors may account for some of discrepant findings of the D-dimer test - first, D-dimer levels decline with time from onset of symptoms, which suggests that patients who present with subacute or chronic symptoms are more likely to have negative D-dimer levels; second, the anatomic extent of thrombosed sinuses may correlate with D-dimer levels, which suggests that patients with lesser clot burden may have false negative D-dimer testing results.

In the view of the above evidence, the following specific recommendations may be summarised (Saposnik et al, 2011):

- In patients with suspected CVST, routine blood studies consisting of a complete blood count, chemistry panel, prothrombin time, and activated partial thromboplastin time should be performed; screening for potential prothrombotic conditions that may predispose a person to CVST (eg, use of contraceptives, underlying inflammatory disease, infectious process) is recommended in the initial clinical assessment;
- A normal D-dimer level according to a sensitive immunoassay or rapid enzyme-linked immunosorbent assay (ELISA) may be considered to help identify patients with low probability of CVST - if there is a strong clinical suspicion of CVST, a normal D-dimer level should not preclude further evaluation;
- In patients with lobar ICH of otherwise unclear origin or with cerebral infarction that crosses typical arterial boundaries, imaging of the cerebral venous system should be performed;
- In patients with the clinical features of idiopathic intracranial hypertension, imaging of the cerebral venous system is recommended to exclude CVST; in patients with headache associated with atypical features, imaging of the cerebral venous system is reasonable to exclude CVST.

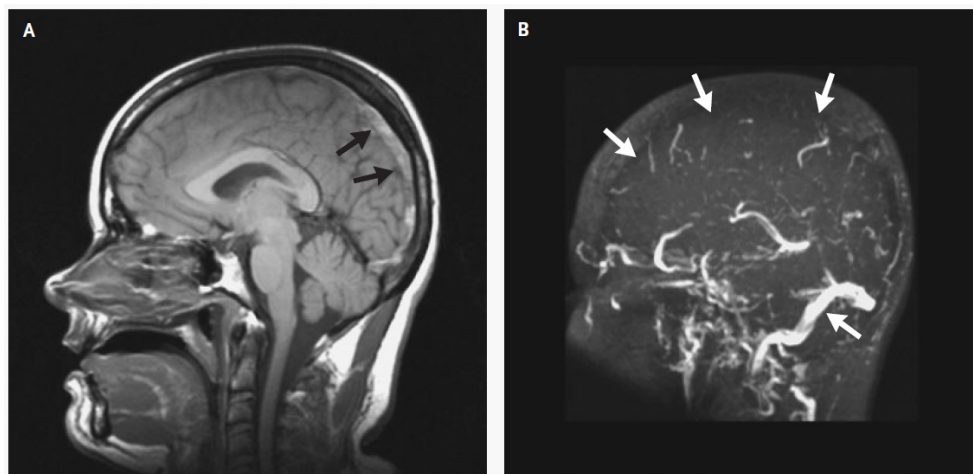


Fig. 3. MRI of Sinus Thrombosis. In Panel A, a T1-weighted MRI scan obtained with the spin-echo technique provides a sagittal view of a hyperintense signal in the thrombosed superior sagittal sinus (arrows). In Panel B, a magnetic resonance venogram obtained without the administration of contrast material reveals the absence of a signal in the superior sagittal sinus (upper arrows) and a normal flow signal in the transverse and sigmoid sinuses (lower arrow) as well as in a number of veins. *Reproduced with the written permission from the paper by Stam (2005).*

*Diagnostic imaging in CVST.* The diagnostic imaging has played an increasing role in the better diagnosis and management of CVST. The aim is to determine vascular and parenchymal changes associated with this medical condition (possibly, the diagnosis is made only with cerebral digital subtraction angiography).

**Noninvasive diagnostic techniques: CT, MRI and ultrasound.** *Computed tomography (CT)* is widely used as the initial neuroimaging test in patients who present with new-onset neurological symptoms such as headache, seizure, mental alteration, or focal neurological signs. CT without contrast is often normal but may demonstrate findings that suggest CVST. Anatomic variability of the venous sinuses makes CT diagnosis of CVST insensitive, with results on a plain CT being abnormal only in about 30% of CVST cases. The primary sign of acute CVST on a non-contrast CT is hyperdensity of a cortical vein or dural sinus. Acutely thrombosed cortical veins and dural sinuses appear as a homogenous hyperdensity that fills the vein or sinus and are most clearly visualized when CT slices are perpendicular to the dural sinus or vein. However, only approximately 30% of CVST demonstrates direct signs of hyperdense dural sinus. Thrombosis of the posterior portion of the superior sagittal sinus may appear as a dense triangle, the dense or filled delta sign. An ischemic infarction, sometimes with a hemorrhagic component, may be seen. An ischemic lesion that crosses usual arterial boundaries (with a hemorrhagic component) or in close proximity to a venous sinus is suggestive of CVST. Subarachnoid hemorrhage is not frequent – it is seen only in up to 0.8% of the CVST patients, and when present, it was localized in the convexity as opposed to the area of the circle of Willis usually observed in patients with aneurysmal rupture. Contrast-enhanced CT may show enhancement of the dural lining of the sinus with a filling defect within the vein or sinus. Contrast-enhanced CT may show the classic “empty delta”

sign, in which a central hypointensity due to absent or very slow flow within the sinus is surrounded by contrast enhancement in the surrounding triangular shape in the posterior aspect of the superior sagittal sinus. This finding may not appear for several days after onset of symptoms but does persist for several weeks. Due to delays or overlooking, CVST may be seen only during the subacute or chronic stage. Compared with the density of adjacent brain tissue, thrombus may be isodense, hypodense, or of mixed density. In this situation, contrast CT or CT venography (CTV) may assist the imaging diagnosis. In general, the *magnetic resonance imaging* (MRI) is more sensitive for the detection of CVST than CT at each stage after thrombosis (**Figure 3**). CVST is diagnosed on MRI with the detection of thrombus in a venous sinus. Findings are variable but may include a “hyperintense vein sign”. Isolated cortical venous thrombosis (Chang et al, 1995) is identified much less frequently than sinus thrombosis. The magnetic resonance signal intensity of venous thrombus varies according to the time of imaging from the onset of thrombus formation. Acute thrombus may be of low intensity. In the first week, venous thrombus frequently appears as isointense to brain tissue on T1-weighted images and hypointense on T2-weighted images owing to increased deoxyhemoglobin. By the second week, thrombus contains methemoglobin, which results in hyperintensity on T1- and T2-weighted images. With evolution of the thrombus, the paramagnetic products of deoxyhemoglobin and methemoglobin are present in the sinus. A thrombosed dural sinus or vein may then demonstrate low signal on gradient-echo and susceptibility-weighted images of magnetic resonance images. The principal early signs of CVST on non-contrast-enhanced MRI are the combination of absence of a flow void with alteration of signal intensity in the dural sinus. MRI of the brain is suggestive of CVST by the absence of a fluid void signal in the sinus, T2 hypointensity suggestive of a thrombus, or a central isodense lesion in a venous sinus with surrounding enhancement. This appearance is the MRI equivalent of the CT empty delta sign. An acute venous thrombus may have hypo-intense signal that mimics a normal flow void. The nature of the thrombus then evolves through a subacute and chronic phase.

Thus, a contrast-enhanced MRI and either CTV or MRV may be necessary to establish a definite diagnosis. The secondary signs of MRI may show similar patterns to CT, including cerebral swelling, edema, and/or hemorrhage. Occasionally, diffusion-weighted imaging (DWI) and perfusion-weighted MRI may assist in making the diagnosis. DWI may show high signal intensity as restricted diffusion- and perfusion-weighted MRI with prolonged transit time. Brain parenchymal lesions of CVST are better visualized and depicted on MRI than at CT. Focal edema without hemorrhage is visualized on CT in about 8% of cases and on MRI in 25% of cases. Focal parenchymal changes with edema and hemorrhage may be identified in up to 40% of patients. Petechial or confluent hemorrhage may also represent an underlying hemorrhagic venous infarction. This may include DWI abnormalities consistent with acute infarction, but the degree of DWI findings may be reduced in venous infarction compared with arterial infarction. An altered enhancement pattern suggestive of collateral flow or of venous congestion may be seen. There are some characteristic patterns of brain parenchymal changes that distinguish CVST from other entities. Also, to some extent, lesions related to specific sinuses are regionally distributed. Brain parenchymal changes in frontal, parietal, and occipital lobes usually correspond to superior sagittal sinus thrombosis. Temporal lobe parenchymal changes correspond to lateral (transverse) and sigmoid sinus thrombosis. Deep parenchymal abnormalities, including thalamic hemorrhage, edema, or intraventricular hemorrhage, correspond to thrombosis of the vein of Galen or straight sinus. MRI signal can also predict radiographic outcome to some extent,

because DWI abnormality within veins or sinus predicts poor recanalization. The *CT venography* (CTV) can provide a rapid and reliable modality for detecting CVST. CTV is much more useful in subacute or chronic situations because of the varied density in thrombosed sinus. Because of the dense cortical bone adjacent to dural sinus, bone artifact may interfere with the visualization of enhanced dural sinus. CTV is at least equivalent to MRV in the diagnosis of CVST. However, drawbacks to CTV include concerns about radiation exposure, potential for iodine contrast material allergy, and issues related to use of contrast in the setting of poor renal function. In some settings, MRV is preferable to CTV because of these concerns. The most commonly used magnetic resonance venography (MRV) techniques are time-of-flight (TOF) MRV and contrast-enhanced magnetic resonance. Phase-contrast MRI is used less frequently, because defining the velocity of the encoding parameter is both difficult and operator-dependent. T2-weighted magnetic resonance image showing mixed hypointensity (white arrow) and isointensity (black arrow) signals representing an acute hemorrhage at left parietal lobe.

The 2D TOF technique is the most commonly used method currently for the diagnosis of CVST, because 2-dimensional TOF has excellent sensitivity to slow flow compared with 3-dimensional TOF. It does have several potential pitfalls in imaging interpretation. Despite the challenges, other sequences such as gradient echo, susceptibility/weighted imaging, and contrast MRI/MRV may assist in these situations. Nonthrombosed hypoplastic sinus will not have abnormal low signal in the sinus on gradient echo or susceptibility-weighted images. The chronic thrombosed hypoplastic sinus will have marked enhanced sinus and no flow on 2-dimensional TOF venography. Contrast-enhanced MRI offers improved visualization of cerebral venous structures (**Figure 4**).



Fig. 4. CVST diagnosis: CT, MRI and venography. MR venography with limited spatial resolution, saturation of flow signal; CT venography; IA venography with hypoplasia vs. occlusion; high anatomical variability. *Reproduced with the written permission from the presentation by Ferro (2010).*

In patients with persistent or progressive symptoms despite medical treatment, repeated neuroimaging (including a CTV or MRV) may help identify the development of a new ischemic lesion, ICH, edema, propagation of the thrombus, or other brain parenchymal lesions. The deep venous system is readily seen on CT and MRI and may be less impacted by artifact because of the separation from bony structures. A potential pitfall at the junction of the straight sinus and vein of Galen on TOF MRI is the appearance of absence of flow if image acquisition is in an axial plane to the skull. This pitfall may be overcome with contrast-enhanced MRI and DWI.

**Invasive diagnostic angiographic procedures.** The *cerebral angiographic procedures* are less commonly needed to establish the diagnosis of CVST given the availability of MRV and CTV. These techniques are reserved for situations in which the MRV or CTV results are inconclusive or if an endovascular procedure is being considered. Cerebral angiography (arteriographic) findings include the failure of sinus appearance due to the occlusion; venous congestion with dilated cortical, scalp, or facial veins; enlargement of typically diminutive veins from collateral drainage; and reversal of venous flow. The venous phase of cerebral angiography will show a filling defect in the thrombosed cerebral vein/sinus. Because of the highly variable cerebral venous structures and inadequate resolution, CT or MRI may not provide adequate visualization of selected veins, especially cortical veins and in some situations the deep venous structures. Hypoplasia or atresia of cerebral veins or dural sinuses may lead to inconclusive results on MRV or CTV and can be clarified on the venous phase of cerebral angiography. Acute dural sinus and cortical vein thrombosis typically causes a delay in cerebral venous circulation, and cerebral angiography will demonstrate delayed and slow visualization of cerebral venous structures. Normally, the early veins begin to opacify at 4 to 5 seconds after injection of contrast material into the carotid artery, and the complete cerebral venous system is opacified in 7 to 8 seconds. If cerebral veins or dural sinuses are not visualized in the normal sequences of cerebral angiography, the possibility of acute thrombosis is suspected. This finding accounts for the observed delayed cerebral perfusion seen with perfusion/weighted MRI with prolonged transit time. The *direct cerebral venography* (DCV) is performed by direct injection of contrast material into a dural sinus or cerebral vein from microcatheter insertion via the internal jugular vein. DCV is usually performed during endovascular therapeutic procedures. In direct cerebral venography, intraluminal thrombus is seen either as a filling defect within the lumen in the setting of nonocclusive thrombosis or as complete nonfilling in occlusive thrombosis. Complete thrombosis may also demonstrate a “cupping appearance” within the sinus. Venous pressure measurements may be performed during direct cerebral venography to identify venous hypertension. Normal venous sinus pressure is <10 mm H<sub>2</sub>O. The extent of parenchymal change correlates with increased venous pressure and with the stage of thrombosis, with changes being maximal in acute thrombosis. *Transfontanellar ultrasound* may be used to evaluate pediatric patients, including newborn or young infants with open anterior or posterior fontanels. Ultrasound, along with transcranial Doppler, may be useful to support the diagnosis of CVST and for ongoing monitoring. Evidence on *perfusion imaging methods* (PIM) using positron emission tomography, although scarce, showed a reduction of the cerebral blood flow after ligation of the superior sagittal sinus with a concomitant venous infarction. An increased regional cerebral blood volume was also observed in a young adult with sagittal sinus thrombosis. A prolonged mean transit time and increased cerebral blood volume have been suggested as venous congestion, contrary to the pattern

observed in patients with an ischemic arterial stroke (prolonged mean transit time with reduction in cerebral blood volume).

Of note, some common pitfalls in the diagnostic imaging should be also mentioned. The positive findings of intraluminal thrombus are the most important feature to a confident diagnosis of CVST by CT or MRI. Unfortunately, these findings are not always evident, and the diagnosis rests on nonfilling of a venous sinus or cortical vein. Given the variation in venous anatomy, it is sometimes impossible to exclude CVST on noninvasive imaging studies. Anatomic variants of normal venous anatomy may mimic sinus thrombosis, including sinus atresia/hypoplasia, asymmetrical sinus drainage, and normal sinus filling defects related to prominent arachnoid granulations or intrasinus septa. Angiographic examination of 100 patients with no venous pathology showed a high prevalence of asymmetrical lateral (transverse) sinuses (49%) and partial or complete absence of one lateral sinus (20%). Flow gaps are commonly seen on TOF MRV images, which sometimes affects their interpretation. The hypoplastic dural sinus may have a more tapering appearance than an abrupt defect in contrast-enhanced images of the sinus. The lack of identification of a thrombus within the venous sinus on MRI or contrast-enhanced MRV or CTV is helpful to clarify the diagnosis. As mentioned, sinus signal-intensity variations may also affect the interpretation of imaging in the diagnosis of CVST. The direct cerebral venography may be difficult to interpret owing to retrograde flow of contrast from the point of injection, and the venous pressure may not be accurate because of relative compartmentalization within the system.

The following specific recommendations for diagnostic imaging in CVST may be summarised (Saposnik et al, 2011):

- Plain CT or MRI is useful in the initial evaluation of patients with suspected CVST, however, a negative plain CT or MRI does not rule out CVST. A venographic study (either CTV or MRV) should be performed in suspected CVST if the plain CT or MRI is negative or to define the extent of CVST if the plain CT or MRI suggests CVST;
- Early follow-up CTV or MRV is recommended in CVST patients with persistent or evolving symptoms despite medical treatment or with symptoms suggestive of propagation of thrombus;
- For patients who present with recurrent symptoms suggestive of CVST and had had a previous CVST, a repeat CTV or MRV is recommended;
- Gradient echo T2 susceptibility-weighted images combined with magnetic resonance can be useful to improve the accuracy of CVST diagnosis;
- Catheter cerebral angiography can be useful in patients with inconclusive CTV or MRV in whom a clinical suspicion for CVST remains high;
- A follow-up CTV or MRV at 3 to 6 months after diagnosis is reasonable to assess for recanalization of the occluded cortical vein/sinuses in stable patients.

### 3.2 Management of CVST - Technological advances and treatment options

**Acute management and treatment of CVST.** A summary algorithm for the diagnosis and management of patients with CVST is provided (**Figure 5**). The initial anticoagulation therapy (AT) has 3 aims in CVST: a) to prevent thrombus growth, b) to facilitate recanalization, and c) to prevent DVT or pulmonary embolism (PE). There is a controversy in the consideration for recommendations regarding AT, because a cerebral infarction with hemorrhagic transformation or ICH is commonly present at the time of diagnosis of CVST,

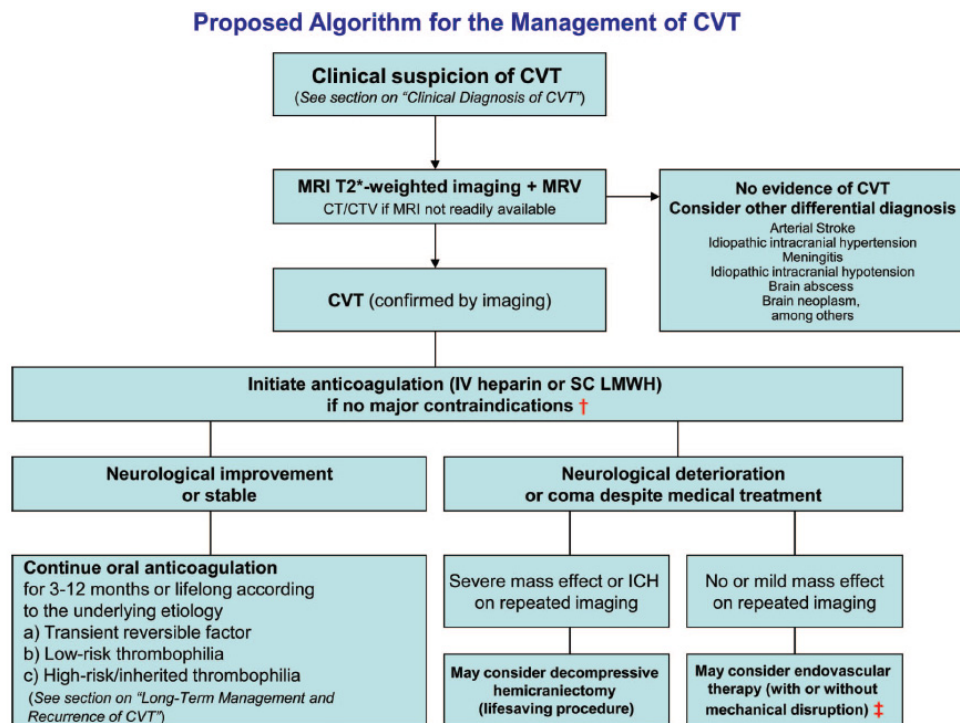


Fig. 5. Algorithm for initial management of CVST. *Symbols and abbreviations:* CVST indicates cerebral venous and sinus thrombosis; LMWH, low molecular weight heparin; Tx, therapy; ICH, intracerebral hemorrhage; CTV, CT venogram; MRV, MR venogram. †Intracranial hemorrhage that occurred as the consequence of CVST is not a contraindication for anticoagulation. ‡Endovascular therapy may be considered in patients with absolute contraindications for anticoagulation therapy or failure of initial therapeutic doses of anticoagulant therapy. *Note:* Anticoagulation remains the principal therapy and is aimed at preventing thrombus propagation and increasing recanalization. This algorithm is not comprehensive, nor applicable to all clinical scenarios and patient management must be individualized. Limited evidence is available on the benefits of decompressive hemicraniectomy and endovascular therapy for the management of CVST as reflected by the low grade and level of recommendations. Anticipated future advances in imaging techniques, new pharmacological agents and endovascular procedures may provide other therapeutic alternatives to be considered in patients with CVST. *Reproduced with the written permission from the paper by Saposnik et al (2011).*

and it may also complicate treatment. A number of observational studies, both prospective and retrospective, are available, primarily from single centers. Not all studies reported specifically on outcomes of anticoagulation treatment, because the majority of patients in most studies were treated with intravenous UFH or low-molecular-weight heparin (LMWH) at the time of diagnosis, with eventual use of vitamin K antagonists. Mortality rates were low, typically less than 10%, often due to the underlying disease (eg, cancer, etc (Knopp, 1995)) rather than CVST and rarely due to ICH. The majority of patients fully recovered neurological



function, and few became disabled. In a retrospective study of 102 patients with CVST, 43 had an ICH. Among 27 (63%) who were treated with dose-adjusted intravenous heparin after the ICH, 4 died (15%), and 14 patients (52%) recovered completely. Of the 13 patients who did not receive heparin, mortality was higher (69%) with lower improvement in functional outcomes (only 3 patients completely recovered). The largest study by far was the ISCVST, which included 624 patients at 89 centers in 21 countries. Nearly all patients were treated with anticoagulation initially, and mortality was 8.3% over 16 months; 79% had complete recovery (modified Rankin scale [mRS] score of 0 to 1), 10.4% had mild to moderate disability (mRS score 2-3) and 2.2% remained severely disabled (mRS score 4-5).<sup>10</sup> Few studies had sufficient numbers of patients not treated with anticoagulation to adequately address the role of anticoagulation in relation to outcome. Data from observational studies suggest a range of risks for ICH after anticoagulation for CVST from zero to 5.4%.

There are two available randomized controlled trials comparing anticoagulant therapy with placebo or open control in patients with CVST confirmed by contrast imaging (cited in Saposnik et al, 2011). Taken together, these trials included only 79 patients. Meta-analysis of these 2 trials revealed a non-statistically significant relative risk of death or dependency with anticoagulation (relative risk 0.46, 95%CI 0.16 to 1.31), with a risk difference in favor of anticoagulation of -13% (95%CI -30% to 3%). The relative risk of death was 0.33 (95%CI 0.08 to 1.21), with a risk difference of -13% (95%CI -27% to 1%). A third randomized trial with 57 women (with puerperal CVST confirmed only by CT imaging) excluded those with hemorrhage on CT. Treatment was with subcutaneous heparin 5000 IU every 6 hours, dose adjusted to an activated partial thromboplastin time 1.5 times baseline for at least 30 days after delivery. Outcome assessment was not blinded. Three patients in the control group either died or had residual paresis compared with none in the heparin group. In the special situation of CVST with cerebral hemorrhage on presentation, even in the absence of anticoagulation, hemorrhage is associated with adverse outcomes. Highlighting this, in 1 trial of nadroparin, all 6 deaths in the trial overall occurred in the group of 29 patients with hemorrhage on their pretreatment CT scan. None of the deaths were attributed to new or enlarged hemorrhage. These 29 patients were equally divided between treatment groups. Thus, cerebral hemorrhage was strongly associated with mortality but not with cerebral bleeding on treatment. Other studies suggested low rates of cerebral hemorrhage after anticoagulation for CVST. In the special situation of a patient with a major contraindication for anticoagulation (such as recent major hemorrhage), the risks and benefits of anticoagulation must be balanced. In these settings, as for venous thrombosis in general, consultation with an expert in anticoagulation management may be appropriate, and low-intensity anticoagulation may be considered if possible in favor of no anticoagulation until such time as it might be safe to use full-intensity anticoagulation. *In conclusion*, limited data from randomized controlled clinical trials in combination with observational data on outcomes and bleeding complications of anticoagulation support a role for anticoagulation in treatment of CVST, regardless of the presence of pretreatment ICH. On the basis of the available data, it is unlikely that researchers will have equipoise on this question, so a new randomized trial may not be feasible. Anticoagulation appears safe and effective. There was consensus in the writing group to support anticoagulation therapy in the management of patients with CVST. If anticoagulation is given, there are no data supporting differences in outcome with the use of UFH in adjusted doses or LMWH in CVST patients. However, in the setting of DVT or PE, a recent systematic review and meta-analysis of 22 studies showed a lower risk of major hemorrhage (1.2% vs. 2.1%), thrombotic complications (3.6% vs. 5.4%), and death (4.5% vs. 6.0%) with LMWH.

**Fibrinolytic therapy (FT)** Although patients with CVST may recover with anticoagulation therapy, 9% to 13% have poor outcomes despite anticoagulation. Anticoagulation alone may not dissolve a large and extensive thrombus, and the clinical condition may worsen even during heparin treatment. Incomplete recanalization or persistent thrombosis may explain this phenomenon. Partial or complete recanalization rates for CVST ranged from 47% to 100% with anticoagulation alone. Unfortunately, most studies reporting partial or complete recanalization at 3 to 6 months have a small sample size. When 4 studies that included 114 CVST patients were combined, partial or complete recanalization at 3 to 6 months was observed in 94 (82.5%). Recanalization rates may be higher for patients who receive thrombolytic therapy (Stolz et al, 2004). In general, thrombolytic therapy is used if clinical deterioration continues despite anticoagulation or if a patient has elevated intracranial pressure that evolves despite other management approaches (Smith et al 1997). Many invasive therapeutic procedures have been reported to treat CVST. These include direct catheter chemical thrombolysis and direct mechanical thrombectomy with or without thrombolysis. There are no randomized controlled trials to support these interventions compared with anticoagulation or with each other. Most evidence is based on small case series or anecdotal reports. Here, we review the studied interventions.

In direct catheter thrombolysis (DCT), a standard microcatheter and microguidewire are delivered to the thrombosed dural sinus through a sheath or guiding catheter from the jugular bulb. Mechanical manipulation of the thrombus with the guidewire increases the amount of clot that might be impacted by the thrombolytic agent, potentially reducing the amount of fibrinolytic agent used. In a retrospective multicenter study of CVST in the United States, 27 (15%) of 182 patients received endovascular thrombolysis. Ten patients were receiving concomitant anticoagulation therapy. Recanalization was achieved in 26 patients (96%), 4 developed an intracranial hemorrhage, and 1 patient (4%) died. A systematic review that included 169 patients with CVST treated with local thrombolysis showed a possible benefit for those with severe CVST, which indicates that fibrinolytics may reduce case fatality in critically ill patients. ICH occurred in 17% of patients after thrombolysis and was associated with clinical worsening in 5%.

The other available options include mechanical thrombectomy/thrombolysis (MTT) techniques. The *balloon-assisted thrombectomy and thrombolysis (BATT)* may be more efficient in cases where (despite above approaches) the sinus thrombosis may still persist the inflated balloon may reduce washout of fibrinolytic agents, potentially lessening the dose of fibrinolytic agents required, the occurrence of hemorrhage, and procedure time. The balloon may be used to perform partial thrombectomy before thrombolysis. A *rheolytic catheter thrombectomy* may be considered in patients with extensive thrombus that persists despite local administration of a fibrinolytic agent. One such device is the AngioJet (MEDRAD, Inc, Warrendale, PA), which uses hydrodynamic thrombolytic action occurring at the tip of the catheter via the Venturi effect from high-velocity saline jets. Thrombus is disrupted and directed down the second lumen of the device. A perforation of the venous sinus wall may occur rarely, at a rate that is unknown but reported in the existing small series. It may be avoided by removal of the AngioJet after partial recanalization of the thrombosis and follow-up with additional microcatheter thrombolysis. The Merci retrieval device (Concentric Medical, Mountain View, CA) has also been used to remove thrombus in the cerebral venous system. This technique also requires direct catheter access to the venous sinus. The small corkscrewshaped device is dispensed via the tip of the catheter, advanced into the thrombus, and then slowly pulled back into the catheter with the adherent

thrombus. Here again, the device may be used to perform partial recanalization, followed by thrombolysis to avoid damaging the wall or trabeculae of the dural sinus. As mentioned above, the evidence available at the present time is anecdotal. The Penumbra System (Penumbra, Inc, Alameda, CA) is a new-generation neuroembolectomy device that acts to debulk and aspirate acute clots. It uses a reperfusion catheter that aspirates thrombus while passing a wire-based separator within the catheter to break up the clot and facilitate aspiration. Only anecdotal evidence for its efficacy is available. The risks associated with use of the Penumbra System for cerebral venous thrombosis are likely similar to those seen with the Merci and AngioJet systems.

As endovascular options for management of venous thrombosis have evolved, surgery has played an increasingly limited role. *Surgical thrombectomy* is needed uncommonly but may be considered if severe neurological or visual deterioration occurs despite maximal medical therapy. In a recent review, among 13 patients with severe CVST who underwent decompressive craniectomy, 11 (84.6%) achieved a favorable outcome (mRS score equal or less than 3). Decompressive craniotomy may be needed as a life-saving measure if a large venous infarction leads to a significant increase in intracranial pressure. Likewise, large hematomas rarely may need to be considered for surgical evacuation if associated with a progressive and severe neurological deficit.

It is to note that, in summary, the use of these direct intrasinus thrombolytic techniques and mechanical therapies is only supported by case reports and small case series. If clinical deterioration occurs despite use of anticoagulation, or if the patient develops mass effect from a venous infarction or ICH that causes intracranial hypertension resistant to standard therapies, then these interventional techniques may be considered. Further, conservative parallel treatment with *aspirin, steroids and antibiotics* may be also discussed. In particular, there are no controlled trials or observational studies that directly assess the role of aspirin in management of CVST. The steroids may have a role in CVST by decreasing vasogenic edema, but may enhance hypercoagulability. In a matched case-control study among the 624 patients in the ISCVST, 150 patients on steroids were compared with matched 150 patients without. Those treated with steroids thus had similar characteristics as control subjects, except they were more likely to have vasculitis. At 6 months, there was a trend toward a higher risk of death or dependence with steroid treatment (OR 1.7, 95%CI 0.9 to 3.3), and this did not differ after the exclusion of those with vasculitis, malignancy, inflammatory disease, and infection. Among those with parenchymal brain lesions on CT/MRI, results were striking, with 4.8-fold increased odds of death or dependence with steroid treatment (95%CI 1.2 to 19.8). Sensitivity analyses that used different analytic approaches yielded similar findings. Also, local (eg, otitis, mastoiditis) and systemic (meningitis, sepsis) infections can be complicated by thrombosis of the adjacent or distant venous sinuses. The management of patients with such suspected infection and CVST should include administration of the appropriate antibiotics and the surgical drainage of infectious sources (ie, subdural empyemas or purulent collections within the paranasal sinuses).

### 3.3 Prognosis of the main clinical outcome and complications

The understanding that CVST is a rare and severe disease with a poor prognosis had to be revised after more recent clinical studies reporting a much better outcome. Mortality rates range from 6–10% and independent survival is reported in 82–90% of patients (as cited in Masuhr et al, 2004). Besides severe underlying medical conditions (e. g. infectious and

malignant causes), coma on admission, clinical worsening after admission and ICH are the most important predictors of a poor outcome. In addition, the site of thrombosis is also a relevant factor and thrombosis of the internal and cerebellar veins carry the worst prognosis. A recently published follow-up study of 40 patients with CVST suggested also a correlation between the degree of recanalization and clinical outcome. Whereas the prevalence of persisting neurological deficits did not differ between patients with complete or partial recanalization, patients with no recanalization had significantly more neurological sequelae (Masuhr et al, 2004).

### 3.3.1 Main outcome and prognosis

There are several studies and reviews on the outcome and prognosis of CVST. The majority of such studies are mainly retrospective. Of the few prospective studies, some did not analyze prognostic factors or performed only a bivariate analysis of such predictors or analyzed specific subgroups of patients. There are only 5 cohort studies that analyzed prognostic factors for the short-term and the long-term outcome of CVST patients (Saposnik et al, 2011).

**Neurological and neuropsychiatric prognosis after the diagnosis of CVST.** Neurological worsening may occur in 23% of patients, even several days after diagnosis. Neurological worsening can feature depressed consciousness, mental status disturbance, new seizure, worsening of or a new focal deficit, increase in headache intensity, or visual loss. About 30% of the patients with neurological deterioration will have new parenchymal lesions when neuroimaging is repeated. Patients with depressed consciousness on admission are more likely to deteriorate. In the view of the *neuropsychiatric sequelae*, the information on the long-term outcome in CVST survivors is limited. Despite the apparent general good recovery in most patients with CVST, approximately one half of survivors feel depressed or anxious, and minor cognitive or language deficits may be observed. Risk factors for poor long-term prognosis in the ISCVST cohort were central nervous system infection, any malignancy, thrombosis of the deep venous system, intracranial hemorrhage on admission CT/MRI, Glasgow Coma Scale score <9, mental status disturbance, age >37 years, and male sex. Brain herniation leading to early death was more frequent in young patients, whereas late deaths due to malignancies and less favorable functional outcome were more frequent in elderly patients. A Glasgow Coma Scale score of 14 to 15 on admission, a complete or partial intracranial hypertension syndrome (including isolated headache) as the only manifestation of CVST, and absence of aphasia were variables associated with a favorable outcome. Below we provide separately a more extensive and detailed encounter of the cognition, behavioural changes and functional outcomes after CVST.

**Death.** Approximately 3% to 15% of patients die in the acute phase of the disorder (*early death*). In the ISCVST (3.4%) of 624 patients died within 30 days from symptom onset; however, in a recent multicenter US study, the mortality (13%) was higher. The risk factors for 30-day mortality were depressed consciousness, altered mental status, and thrombosis of the deep venous system, right hemisphere hemorrhage, and posterior fossa lesions. The main cause of acute death with CVST is transtentorial herniation secondary to a large hemorrhagic lesion, followed by herniation due to multiple lesions or to diffuse brain edema. *Status epilepticus*, medical complications, and PE are among other causes of early death. The deaths after the acute phase (*late death*) are related mainly to the underlying conditions, in particular malignancies. In the ISCVST study, a complete recovery at last follow-up (median 16 months) was observed in 79% of the patients; however, the overall death rate was 8.3% and the dependency rate of 5.1% at the end of follow-up was observed.

In a systematic review that included both retrospective and prospective studies, overall mortality was 9.4%, and the proportion of dependency (mRS score  $\geq 3$  or Glasgow Outcome Scale score  $\leq 3$ ) was 9.7%. Two new studies were reported after this systematic review. In the Pakistan-Middle East registry,<sup>63</sup> the dependency rate (mRS score  $\geq 3$ ) was higher (11%), whereas in the US multicenter registry, 28% of patients were dependent at 12 months. Of note, some studies include patients transferred to tertiary care centers, whose strokes are usually more severe, with the potential for a referral bias. Among the 7 cohort studies (including the prospective part of retrospective/prospective studies in which information can be analyzed separately), the overall death and dependency rate was 15% (95%CI 13% to 18%).

### 3.3.2 Early and late complications – Management and prevention

Up to 40% of patients with CVST present with isolated *intracranial hypertension*. This is characterized by diffuse brain edema, sometimes seen as slit ventricles on CT scanning. Clinical features include progressive headache, papilledema, and third or sixth nerve palsies. Intracranial hypertension is primarily caused by venous outflow obstruction and tissue congestion compounded by CSF malabsorption. No randomized trials are available to clarify the optimal treatment; however, rational management of intracranial hypertension includes a combination of treatment approaches. First, measures to reduce the thrombotic occlusion of venous outflow, such as anticoagulation and possibly thrombolytic treatment, may result in resolution of intracranial hypertension. Second, reduction of increased intracranial pressure can be accomplished immediately by lumbar puncture with removal of CSF until a normal closing pressure is achieved. Unfortunately, lumbar puncture requires temporary cessation of anticoagulants, with an attendant risk of thrombus propagation. Despite the lack of randomized clinical trials, acetazolamide is a commonly used therapeutic alternative for the treatment of intracranial hypertension with CVST. It may have a limited role in the acute management of intracranial hypertension for patients with CVST. Acetazolamide, a carbonic anhydrase inhibitor, is a weak diuretic and decreases production of CSF. Serial lumbar punctures may be necessary when hypertension is persistent. In refractory cases, a lumboperitoneal shunt may be required. Because prolonged pressure on the optic nerves can result in permanent blindness, it is of paramount importance to closely monitor visual fields and the severity of papilledema during the period of increased pressure. Ophthalmologic consultation is helpful for this. Although rarely required, optic nerve fenestration is a treatment option to halt progressive visual loss. Decompressive craniectomy has been used in patients with malignant arterial stroke to treat elevated intracranial pressure unresponsive to conventional treatment. In a pooled analysis of randomized trials, surgical decompression within 48 hours of stroke onset reduced case fatality and improved functional outcome. Limited evidence is available on the role of decompressive craniectomy in CVST with either brain edema, venous infarction, neurological deterioration, or impending cerebral herniation. A disadvantage of craniectomy is that it precludes anticoagulation for the immediate postoperative period.

**Seizures** are present in 37% of adults, 48% of children, and 71% of newborns who present with CVST. No clinical trials have studied either the optimal timing or medication choice for anticonvulsants in CVST. Whether to initiate anticonvulsants in all cases of CVST or await initial seizures before treatment is controversial. Because seizures increase the risk of anoxic damage, anticonvulsant treatment after even a single seizure is reasonable. In the absence of seizures, the prophylactic use of antiepileptic drugs may be harmful (the risk of side effects

may outweigh its benefits). A few studies have reported the occurrence and characteristics of patients with seizures accompanying CVST. One study reported that 32% out of 91 patients presented with seizures and 2% developed them during hospitalization; only 9.5% developed late seizures, and seizures were not a predictor of prognosis at 12 months. Early seizures were 3.7-fold more likely (95%CI 1.4 to 9.4) in those with parenchymal lesions on CT/MRI at diagnosis and 7.8-fold more likely (95%CI 0.8 to 74.8) in those with sensory defects. A more recent report from the ISCVST showed 245 (39%) of 624 patients presented with seizures and 43 (6.9%) experienced early seizure within 2 weeks after diagnosis. Besides seizures on presentation, only a supratentorial parenchymal lesion on CT/MRI at diagnosis (present in 58%) was associated with occurrence of early seizures (OR 3.1, 95%CI 1.6 to 9.6). Furthermore, among those with a supratentorial lesion and no presenting seizure, use of antiepileptic drugs was associated with a 70% lower risk of seizures within 2 weeks, although this was not statistically significant (OR 0.3, 95%CI 0.04 to 2.6). On the basis of these findings, the authors suggested the prescription of antiepileptic agents in acute CVST patients with supratentorial lesions who present with seizures. Hydrocephalus The superior sagittal and lateral dural sinuses are the principal sites for CSF absorption by the arachnoid granulations, highly vascular structures that protrude across the walls of the sinuses into the subarachnoid space and drain into the venous system. In CVST, the function of the arachnoid granulations may be impaired, potentially resulting in failure of CSF absorption and communicating hydrocephalus (6.6%).

**Obstructive hydrocephalus** is a less common complication of CVST and results from hemorrhage into the ventricular system. This is typically associated with thrombosis that involves the internal cerebral veins and may be associated with thalamic hemorrhage. This syndrome is well described in term neonates but occurs at all ages. Neurosurgical evacuation of CSF with ventriculostomy, or in persistent cases, ventriculoperitoneal shunt, is necessary. The brain is under increased venous pressure, and tissue perfusion is at increased risk compared with other situations with obstructive hydrocephalus. Therefore, close monitoring and neurosurgical consultation are important, because intervention may be required at lesser severities of ventricular enlargement.

**Recurrence of CVST.** The overall risk of recurrence of any thrombotic event (*CVST or systemic*) after a CVST is 6.5% per year. The risk of other manifestations of VTE after CVST ranges from 3.4% to 4.3% on the basis of the largest studies of this medical condition (Ferro et al, 2004; Saposnik et al, 2011). Patients with severe thrombophilia have an increased risk of VTE. The secondary Prevention of CVST and Other VTE Events DVT/PE and CVST share some similarities. The chronic and transient risk factors appear to be similar, although women are more likely to have CVST and selected thrombophilia subtypes may differ between CVST and DVT/PE. In the ISCVST cohort, the overall rate of recurrent CVST or other VTE recurrence was 4.1 per 100 person-years, with male sex and polycythemia/thrombocythemia being the only independent predictors found. The same study reported a steady increase in the cumulative risk of thrombotic recurrences not influenced by the duration of anticoagulation, which emphasizes the need for a clinical trial to assess the efficacy and safety of short versus extended anticoagulant therapy. Given that systemic VTE after CVST is more common than recurrent CVST, one may reasonably adopt the VTE guidelines for prevention of both new VTE and recurrent CVST. However, each individual patient should undergo risk assessment and the patient's risk level and preferences regarding long-term anticoagulation treatment, the risk of bleeding, and the risk

of thrombosis without anticoagulation should then be considered. In particular, when considered in a more detail, the secondary prevention strategies focus on preventing recurrence of CVST or other VTE in those CVST patients at high risk of such outcomes. There are no available risk stratification schemes in CVST. There are no randomized clinical trials of long-term prevention of first or recurrent CVST. Because there are no secondary prevention trials of anticoagulation in adults with CVST, evaluation of prevention strategies can only be performed with observational studies that evaluate CVST or VTE recurrence. In a cohort of 154 patients treated at Mayo Clinic between 1978 and 2001, 56 patients initially received both heparin and warfarin, 12 received heparin only, and 21 received warfarin only. Seventy-seven (50%) were treated with warfarin for an average of 9 months, with 25 committed to lifelong therapy. During 36 months of follow-up (464 patient-years), there were 23 recurrent VTEs in 20 patients (13%), the majority in the first year. Ten patients had recurrent CVST (2.2 per 100 patient-years), and 11 had DVT or PE (2.8 per 100 patient-years). Nine of the recurrent events occurred while the patients were taking warfarin. After 8 years of follow-up, there was no impact of warfarin on survival or recurrence-free survival. In a cohort of 54 CVST patients treated consecutively at University Hospital Gasthuisberg, Leuven, Belgium, 8 (14.8%) had a recurrence of VTE (7 with DVT or PE and one with CVST and mesenteric vein thrombosis) over a median of 2.5 years of follow-up (4.5 per 100 patient-years). Median time to recurrence was 2.5 months (range 2 weeks to 4 years). Only 2 of these 8 patients were taking anticoagulants at the time of recurrence, 1 with an international normalized ratio (INR) of 1.6 and the other with an INR of 2.1. Among the 6 patients with recurrent VTE who were not taking anticoagulants, recurrence occurred between 2 weeks and 10 months after the index event. Those with recurrence more often had a thrombophilic disorder, had a history of DVT, and had not received oral anticoagulation because of perceived contraindications. In the ISCVST study, among 624 patients with CVST, there were 14 (2.2%) recurrent CVSTs and 27 (4.3%) other thrombotic events (16 DVT, 3 PE, 2 ischemic stroke, 2 transient ischemic attack, and 4 acute limb ischemia) over a mean follow-up of 16 months. Seventeen (41.5%) of the 41 patients with recurrent or other thrombotic events were receiving anticoagulants, but the type of anticoagulation and the number who were receiving therapeutic doses of anticoagulation were unknown. It was not reported whether anticoagulation was given long-term and whether recurrent events differed based on its use. The Cerebral Venous Thrombosis Portuguese Collaborative Study Group (VENOPORT) evaluated outcomes for 142 CVST patients, of whom 51 were retrospectively enrolled and 91 were prospectively enrolled. There were 2 (2%) recurrent CVSTs and 10 (8%) other arterial or venous thrombotic events (maximum 16 years of follow-up for the retrospective cases and 12 months of follow-up for prospective cases). For the prospectively followed cases, the incident risk of a thrombotic event was 4% per year (5 thrombotic events in 4 patients: 2 DVTs, 1 PE, 1 ischemic stroke, and 1 acute limb ischemia). Three of these events occurred with anticoagulation use, although the INR levels were unknown at the time of the event. In addition, all of these events occurred within 12 months of the index CVST. A cohort of 77 CVST patients diagnosed in France between 1975 and 1990 was followed up for 63 months. Nine (11.7%) had a recurrence of CVST, 8 during the first 12 months, and none were receiving anticoagulation at the time of recurrence. Eleven patients (14.3%) had other thrombotic events, including retinal vein thrombosis, PE, and arterial thromboses. Use of anticoagulation at the time of recurrent thromboses that were not CVSTs was not reported. More recently, 145 patients with a first CVST were followed up for a median of 6 years after discontinuation of anticoagulation therapy. CVST recurred in 5 patients (3%),

and other manifestations of VTE (*defined as DVT of the lower limbs or PE*) were seen in 10 additional patients (7%). The recurrence rate accounted for 3.4% of all VTEs in the first 16 months (or 2.03 per 100 person-years; 95%CI 1.16 to 3.14) and 1.3% of CVSTs in the first 16 months (or 0.53 per 100 person-years; 95%CI 0.16 to 1.10). Approximately half of the recurrences occurred within the first year after discontinuation of anticoagulant therapy. Mild thrombophilia abnormalities were not associated with recurrent CVST, but severe thrombophilia showed an increased risk of DVT or PE. In summary, the prevalence of CVST recurrence was similar in the Italian and ISCVST studies (1.3% and 2.2%, respectively) at the 16-month follow-up.

In patients with DVT or PE, increasing evidence suggests there is clinical utility to D-dimer measurement when used to define risk of recurrent VTE. For example, in a randomized controlled trial (n=608), patients with an abnormal D-dimer level 1 month after the discontinuation of anticoagulation had a significant incidence of recurrent VTE (15% versus 2.9%), which was reduced by the resumption of anticoagulation (compared with those not receiving vitamin K antagonists). During 1.4 years of follow-up, 120 subjects with an abnormal D-dimer level were randomized to no anticoagulation and 15% in this group developed a recurrent VTE. Of 103 patients with abnormal D-dimer randomized to resume anticoagulation, only 2.9% had a recurrent VTE. Although the study was randomized, it was unblinded, and D-dimer levels were only obtained once. In addition, there were no subjects with CVST and no similar studies in CVST patients. Although the clinical utility of D-dimer for longer-term anticoagulation for VTE secondary prevention appears promising, the lack of standardization of D-dimer assays may limit their clinical applicability and reliability.

In particular, thrombophilias may be hereditary or acquired, and hereditary thrombophilias have been stratified as mild or severe on the basis of the risk of recurrence in very large family cohorts. Among VTE patients, the hereditary thrombophilias with the highest cumulative recurrence rates for VTE in the absence of ongoing anticoagulation have been deficiencies of antithrombin, protein C, and protein S, with a 19% recurrence at 2 years, 40% at 5 years, and 55% at 10 years. Homozygous prothrombin G20210A, homozygous factor V Leiden, deficiencies of protein C, protein S, or antithrombin, combined thrombophilia defects and antiphospholipid syndrome are categorized as severe. Interestingly, the more common hereditary thrombophilias, such as heterozygous factor V Leiden and prothrombin G20210A or elevated factor VIII, have a much lower risk of recurrence (7% at 2 years, 11% at 5 years, and 25% at 10 years) and could be categorized as mild. Hyperhomocysteinemia, a common hereditary or acquired risk factor for VTE, was not significantly associated with a high risk of recurrence. In addition, the annual incidence and the risk of recurrence increased markedly in those with combined thrombophilic defects, described as double heterozygous/homozygous. There are several important points regarding the hereditary thrombophilia data described above. First, the familial nature of these deficiencies of protein C, S, or antithrombin was clearly established, which distinguishes these patients from those with sporadic or acquired abnormalities. Second, testing for deficiencies of protein C, S, and antithrombin must be performed at least 6 weeks after a thrombotic event and then confirmed with repeat testing and family studies. In addition, protein C and S functional activity and antithrombin levels are difficult to interpret during treatment with warfarin. Therefore, testing for these conditions is generally indicated 2 to 4 weeks after completion of anticoagulation. Lastly, clearly established deficiencies of proteins C, S, and antithrombin are relatively uncommon. Antiphospholipid antibody syndrome (Atanassova, 2007) is an



acquired thrombophilia associated with specific laboratory criteria (lupus anticoagulant, anticardiolipin antibody, and anti- $\beta_2$ -glycoprotein I) and a history of a venous or arterial event or fetal loss. Caution must be taken when the results of antiphospholipid antibody testing are interpreted. A normal result may occur at the time of the clinical presentation, which rules out antiphospholipid antibody syndrome. On the other hand, abnormal tests may occur transiently due to the disease process, infection, certain medications (antibiotics, cocaine, hydralazine, procainamide, quinine, and others), or unknown causes. Approximately 5% of the general population at any given time has evidence of abnormal tests, and these mainly have no clinical consequence. A diagnosis of antiphospholipid syndrome requires abnormal laboratory testing on 2 or more occasions at least 12 weeks apart. Patients diagnosed with antiphospholipid syndrome have an increased risk of recurrent thrombotic events; however, test results cannot predict the likelihood of complications, their type, or their severity in a particular patient. Although there are no prospective studies that report recurrence rates for CVST specifically, the high risk of recurrent VTE with this disorder meets the definition of severe thrombophilia. The Duration of Anticoagulation Study Group reported a 29% recurrence of VTE in patients with anticardiolipin antibodies versus 14% in those without over 4 years and the risk increased with the titer of the antibodies. In a randomized controlled trial of warfarin for 3 months versus extended treatment for 24 months after first-ever idiopathic DVT or PE, the presence of antiphospholipid antibodies was associated with a 4-fold increased risk of recurrence (hazard ratio [HR] 4.0, 95%CI 1.2 to 13), and the presence of a lupus anticoagulant was associated with a 7-fold increased risk (HR 6.8, 95%CI 1.5 to 31) in the placebo group. Further recommendations, with associated class and level of evidence, are provided in the recent guidelines by Saposnik et al (2011). In particular, a testing for prothrombotic conditions, including protein C, protein S, antithrombin deficiency, antiphospholipid syndrome, prothrombin G20210A mutation, and factor V Leiden, can be beneficial for the management of CVST patients.

**Other late complications.** *Headache* is common and occurs in about half of the patients during the follow-up. In general, headaches are primary and not related to CVST. In the Lille study, 53% of patients had residual headache, 29% fulfilled criteria for migraine, and 27% had headache of the tension type. In VENOPORT, 55% of patients reported headaches during the follow-up, and these were mild to moderate in 45%. At follow-up, severe headaches that required bed rest or hospital admission were reported in 14% of patients in the ISCVST and 11% in VENOPORT. In patients with persistent or severe headaches, appropriate investigations should be completed to rule out recurrent CVST. Occasionally, MRV may show stenosis of a previously occluded sinus, but the clinical significance of this is unclear. Headache during follow-up is more common among patients who present acutely as having isolated intracranial hypertension. In these patients, if headache persists and MRI is normal, lumbar puncture may be needed to exclude elevated intracranial pressure. *Focal or generalized post-CVST seizures* can be divided into early or remote (2 weeks after diagnosis) seizures. On the basis of case series, remote seizures affect 5% to 32% of patients. Most of these seizures occur in the first year of follow-up. In ISCVST, 11% of the patients experienced remote seizures (36 patients by 6 months, 55 by 1 year, and 66 by 2 years). Risk factors for remote seizures were hemorrhagic lesion on admission CT/MRI (HR 2.62, 95%CI 1.52 to 4.52), early seizure (HR 2.42, 95%CI 1.38 to 4.22), and paresis (HR 2.22, 95%CI 1.33 to 3.69). Five percent of the patients had post-CVST epilepsy. Post-CVST epilepsy was also associated with hemorrhagic lesion on admission CT/MRI (OR 6.76,

95%CI 2.26 to 20.41), early seizure (OR 3.99, 95%CI 1.16 to 11.0), and paresis (OR 2.75, 95%CI 1.33 to 6.54). Initiation of antiepileptic drugs for a defined duration is recommended to prevent further seizures in patients with CVST and parenchymal lesions who present with a single seizure. *Severe visual loss* due to CVST is rare (2% to 4%). Papilledema can cause transient visual impairment, and if prolonged, optic atrophy and blindness may ensue. Visual loss is often insidious, with progressive constriction of the visual fields and relative sparing of central visual acuity. Visual deficits are more common in patients with papilledema and those who present with increased intracranial pressure. Delayed diagnosis is associated with an increased risk of later visual deficit. Patients with papilledema or visual complaints should have a complete neuroophthalmological study, including visual acuity and formal visual field testing. Further, a thrombosis of the cavernous, lateral, or sagittal sinus can later induce a *dural arteriovenous fistula*. A pial fistula can also follow a cortical vein thrombosis. The relationship between the 2 entities is rather complex, because (1) dural fistulas can be a late complication of persistent dural sinus occlusion with increased venous pressure, (2) the fistula can close and cure if the sinus recanalizes, and (3) a preexisting fistula can be the underlying cause of CVST. The exact frequency of dural fistula after CVST is not known because there are no cohort studies with 22 long-term angiographic investigation. The incidence of dural arteriovenous fistula was low in cohort studies without systematic angiographic follow-up (1% to 3%). A cerebral angiogram may help identify the presence of a dural arteriovenous fistula.

Specific recommendations for management of CVST and its complications can be summarised as follows (Saposnik et al, 2011):

- Patients with CVST and a suspected bacterial infection should receive appropriate antibiotics and surgical drainage of purulent collections of infectious sources associated with CVST when appropriate;
- In patients with CVST and increased intracranial pressure, monitoring for progressive visual loss is recommended, and when this is observed, increased intracranial pressure should be treated urgently;
- In patients with CVST and a single seizure with parenchymal lesions, early initiation of antiepileptic drugs for a defined duration is recommended to prevent further seizures;
- In patients with CVST and a single seizure without parenchymal lesions, early initiation of antiepileptic drugs for a defined duration is probably recommended to prevent further seizures;
- In the absence of seizures, the routine use of antiepileptic drugs in patients with CVST is not recommended;
- For patients with CVST, initial anticoagulation with adjusted-dose UFH or weight-based LMWH in full anticoagulant doses is reasonable, followed by vitamin K antagonists, regardless of the presence of ICH;
- Admission to a stroke unit is reasonable for treatment and prevention of complications of patients with CVST;
- In CVST patients with increased intracranial pressure, it is reasonable to initiate treatment with acetazolamide. Other therapies (lumbar puncture, optic nerve decompression, or shunts) can be effective if there is progressive visual loss;
- Endovascular intervention may be considered if deterioration occurs despite intensive anticoagulation treatment;

- In patients with neurological deterioration due to severe mass effect or intracranial hemorrhage causing intractable intracranial hypertension, decompressive hemicraniectomy may be considered;
- For patients with CVST, steroid medications are not recommended, even in the presence of parenchymal brain lesions on CT/MRI, unless needed for another underlying disease;
- The current recommendations for VTE patients call for indefinite anticoagulation (adjusted-dose warfarin INR 2.0 to 3.0 or heparin) for patients with antiphospholipid syndrome;
- In patients with a history of CVST who complain of new, persisting, or severe headache, evaluation for CVST recurrence and intracranial hypertension should be considered.

### 3.3.3 Clinical prediction rules (CPRs) or risk score models in CVST

Although the overall outcome of CVST is favourable, about 15% of the patients become dependent or die. Clinical prediction rules (CPRs) or risk stratification models and scores (McGinn et al, 2000; McNally et al, 2010) might improve the ability to inform doctors about the individual prognosis of different disease conditions, including CVST. There are specific methodological standards that are applied to CPRs before their use in the clinical practice can be recommended. Ideally, a rule or scale undergoes three steps: derivation, narrow and broad validation, and impact analysis (randomised controlled trial assessing its effectiveness and cost-effectiveness) (McGinn et al, 2000). In this way, if a rule is applied, it is possible to further identify those CVST patients who could benefit from more intensive monitoring and/or invasive interventions at most. For instance, Barinagarrementeria et al (1992) proposed a prognostic scale based on clinical, CT and cerebrospinal fluid (CSF) analysis. The presence of coma or bilateral pyramidal signs was rated at 3, that of generalized seizures at 2 and that of meningeal signs, bilateral lesions on CT scan and haemorrhagic CSF all at 2 points. The prognosis was found to be 100% good when total score was <3, usually good (85%) with a score of 4-5, usually bad (90%) with a score of 6-8 and 100% bad with a score of >9. This scale, however, has not been consistently validated further in other CVST datasets. Another risk score model to predict a poor outcome has also been derived and validated. The score ranged from 0 (lowest risk) to 9 (highest risk), and a cut-off value equal or higher than 3 indicated a higher risk of death or dependency at 6 months. One point was assigned for male sex, presence of decreased level of consciousness, or ICH while 2 points indicated the presence of malignancy, coma, or thrombosis of the deep venous system. The discrimination performance, or area under the receiver operating characteristics (ROC) curve (AUC or c-statistics) in the derivation cohort was 85.4%, 84.4%, and 90.1% in the validation cohorts samples (Ferro et al, 2004; Dentali et al, 2006). Another study incorporated the age above 37 years and central nervous system infection as additional risk factors into the latter model. The authors validated the score in 90 patients and obtained  $AUC_{ROC}=81\%$  to predict mortality (with sensitivity of 88% and specificity of 70% at a cut-off value equal or above 14) (Koopman et al, 2009). Notably, further validation studies are needed to better quantify and estimate the discrimination and calibration performance and overall generalisability of the above clinical prediction rule in other populations and settings.

### 3.4 Cognition, behavioural changes and functional outcomes after CVST

For many years CVST has been considered rare and lethal disease, diagnosed postmortem. The use of neuroimaging techniques as computer tomography, the magnetic resonance

imaging and the cerebral angiography has made possible the early diagnoses and has changed the knowledge about this condition (Boussier et al., 2007; Breteau et al., 2003; Preter et al., 1996). The increase of the data about it in the scientific literature enlarges the aspects studied and poses new questions. One of these questions is related to the functional outcome after CVST and the impact of cognitive impairments and behavioural changes on it. Due to the heterogeneity of study methodology and design, it is very difficult to compare the obtained results. Another important obstacle is due to the differences in the diagnostic process, in the extent of control for the underlying causes for CVST, for the clinical presentations and the treatment strategy.

Most of the authors reported good functional outcome after CVST (Cakmak et al., 2003; de Bruijn et al., 2001; Ferro et al., 2001; Ferro et al., 2002; Hameed et al., 2006; Kirmani et al., 2005). In a 77 months follow-up 86% of the patients recovered without neurological sequelae (Preter et al., 1996). The conclusions from the largest, for the time being, international study - ISCVST (Ferro et al., 2004) and from a large systematic review of 19 papers on CVST (Dentali et al., 2006) were for a better prognosis than reported previously. Most of the patients examined by Stolz et al. (2004) showed significant improvement on hospital discharge and 89% of them had significant functional improvement 12 months after the discharge. A review of long-term follow-up studies found that from 1943 patients examined, only 180 had poor recovery with permanent neurological deficit (Dentali et al., 2006). At the same time Bender et al. (2006) found that the severe CVST cases had not been studied in details and that cognitive impairments could influence negatively the quality of life of survived patients. De Bruijn et al. (2000) reported less favorable CVST outcome than reported previously.

CVST is a condition that requires a prompt diagnose and treatment. The mode of onset of CVST is acute in 37,2% and sub-acute in 55,5% of the participants in ISCVST. Probably this is the reason for the lack of data about the cognitive functioning of the patients. But it is difficult to explain the absence of neuropsychological techniques from the set of methods, assessing the long-term recovery of surviving patients. Most of the outcome studies of CVST do not include testing of cognition and assessment of behavioural changes (Breteau et al., 2003; Cakmak et al., 2003; de Bruijn et al., 2001; Ferro et al., 2001; Ferro et al., 2002; Stolz et al., 2004).

The assessment of the extent of functional recovery after CVST is limited. The outcome after CVST is traditionally described by modified Rankin Scale score, that gives information only about the patient motor activity and the capacity for carrying out previous activities. Some of the studies report data received by mail or by phone.

Abulia, executive deficits, and amnesia may result from thrombosis of the deep venous system, with bilateral panthalamic infarcts. Memory deficits, behavioral problems, or executive deficits may persist. The importance of more detailed examination and neuropsychological testing could be confirmed by a paper, reporting the results of functionally independent patients, having long-term symptoms with negative impact on their everyday functioning: 75% of patients, included in this 63 months follow-up, reported concentration impairments (Koopman et al., 2009).

Aphasia was a clinical feature of CVST, found in 19% of the participants from 21 countries in ISCVST study (Ferro et al., 2004). Aphasia, in general of the fluent type, results from left lateral sinus thrombosis with temporal infarct or hemorrhage. Recovery is usually favorable, but minor troubles in spontaneous speech and naming might persist. Cognitive assessment for aphasia, apraxia and working memory found aphasia in 3 patients and working memory deficit in 6 out of 34 patients in a follow-up study (Buccino et al., 2003). Preter et al. (1996)

report 1 patient with aphasia and 3 patients with memory loss and dementia in a 78 months' follow-up of 77 patients with CVST. A detailed neuropsychological testing of participants in a long-term CVST outcome study showed that 35% of patients had abnormal performance on two or more cognitive tests, 33% - had impairments in two or more cognitive functions. Prevalence was found for visuospatial, constructive and language impairments (de Bruijn et al., 2000). Another interesting finding is the presence of cognitive impairments in patients with low scores for functional health. This report warrants for more detailed long-term assessment of CVST patients, including cognitive testing, because cognition is an important factor for everyday functioning and for the level of quality of life. The data about behavioural changes and the quality of life are even scarcer than these, related to cognitive domains. Psychiatric symptoms are rarely described during the diagnostic phase (Boussier et al., 2007). Behavioural changes are mentioned in the study of Preter et al., (1996). Data exist about depression and fatigue as long-term sequelae after CVST (Koopman et al., 2009; Buccino et al., 2003). Assessment with questionnaires for quality of life and for well-being after CVST is very rare as well (Bender et al., 2007).

#### 4. Conclusions

The main findings of this review were that all age groups can be affected by CVST and the large sinuses such as the superior sagittal sinus are most frequently involved. Extensive collateral circulation within the cerebral venous system allows for a significant degree of compensation in the early stages of thrombus formation. Systemic inflammatory diseases and inherited as well as acquired coagulation disorders are frequent causes, although in up to 30% of cases no underlying cause can be identified. The diagnosis is usually made by venographic studies with computer tomography (CT or CTV) or magnetic resonance imaging (MRI or MRIV) to demonstrate obstruction of the venous sinuses or cerebral veins by a thrombus. The MRI with venography (MRIV) is the investigation of choice; computed tomography alone will miss a significant number of cases. Additionally, the use of such precise neuro-imaging techniques gives the possibility for early diagnosis and treatment of emerging neuropsychological impairments in the set of the clinical symptoms in CVST; for instance, a cognitive deficit as part of the long-term outcome; a range of psychiatric complications and, last but not least, to collect data and explore the various aspects of the health-related quality of life or HRQOL) in such patients. It should be noted that the neuropsychological impairments that could be present during CVST are not well known, including various aspects of the assessment of the eventually impaired mental status. For instance, various data exist about disorientation, lack of coordination, incapacity to follow commands, neglect, apraxia, recent memory impairments and language impairments, among others. In the same time, very little is known about the long term outcome of CVST - for instance, it has been observed that many patients experience some persistent neurologic and cognitive deficits, but data are scarce and difficult to collect and summarise. The management of CVST includes treatment of the underlying condition; symptomatic treatment; the prevention or treatment of complications of increased intracranial pressure, ICH, or venous infarction; and typically, anticoagulation therapy. It has now been conclusively shown that intravenous heparin is the first-line treatment for cerebral venous sinus thrombosis because of its efficacy, safety and feasibility. Local thrombolysis may be indicated in cases of deterioration, despite adequate heparinisation. This should be followed by oral anticoagulation for 3-6 months. The prognosis of cerebral venous sinus thrombosis is

generally favourable. A high index of clinical suspicion is needed to diagnose this uncommon condition so that appropriate treatment can be initiated. Complications, in a short- and a long-term, include but are not limited to cognition and behavioural changes.

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